AF

CASE :**LD0268 US - NP**

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Anastasia P. Winslow		Sept. 25, 2006
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
FRANCIS LEE, ET AL
APPLICATION NO: **10/091,061**
FILED: **03/05/2002**
FOR: **COMBINATION OF EPOTHILONE ANALOGS AND CHEMOTHERAPEUTIC AGENTS FOR THE TREATMENT OF PROLFERATIVE DISORDERS.**

ART UNIT: **1617**
EXAMINER: **CHONG, YONG SOO**

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REPLY BRIEF

Sir:

This reply brief is submitted in response to the Examiner's Answer, dated July 25, 2006, in the appeal of the present application to the Board of Patent Appeals and Interferences.

I. STATUS OF THE CLAIMS

Claims 117-130 are on appeal.

All remaining claims (1-116) have either been canceled or stand rejected and are not being appealed.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed on this appeal:

1. Whether claims 117-125 are nonobvious under 35 U.S.C. 103(a) over Danishefsky (US 6,867,305) in view of Miwa *et al.* (*European Journal of Cancer*, Vol. 34, No. 8, pp 1274-1281, 1998).

2. Whether claims 117-130 are nonobvious under 35 U.S.C. 103(a) over Vite (WO 99/02514) in view of The Merck Index (12th Edition, pp MISC-10, 1996), and Miwa *et al.* (*European Journal of Cancer*, Vol. 34, No. 8, pp 1274-1281, 1998).

III. ARGUMENT

A *prima facie* case of obviousness has not been established. In the present rejections, the Examiner has not met the required legal standard for establishing *prima facie* obviousness -- not as to motivation to combine references, reasonable expectation of success, or teaching or suggestion of all the claim limitations.

At page 6, lines 9-12, of the Examiner's Answer ("EA"), it is acknowledged that "[t]he prior art does not expressly disclose the employment of the instant particular compound with the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine in a pharmaceutical composition and a method for treating cancer."

However, the Examiner argues, at page 7, lines 14-18 (EA), that "one of ordinary skill in the art would have reasonably expected that combining the specific anti-cancer agents such as fluorouracil (5-FU) and/or capecitabine and the instant compound ...

would improve the therapeutic effects for treating the same, and/or would introduce *additive therapeutic effects* in treating the same." (Emphasis added)

Appellant's reply is threefold. First, there is no evidence in the record, *e.g.*, via motivation to combine or otherwise, upon which the Examiner relies to make this assertion regarding what one skilled in the art would have reasonably expected. The Examiner is making an unsupported conclusory statement, without basis in the patent literature or otherwise. There is no evidence in the record that at the time of appellant's invention, one skilled in the field would expect a combination of capecitabine with ixabepilone to improve the therapeutic effects for treating cancer achievable with either of these agents alone.

Second, the Examiner's arguments are not directed to the language of the claims on appeal. Each of the claims on appeal recite a synergistic or greater than additive effect in treating certain types of cancer with ixabepilone in combination with capecitabine. However, as is clear from the above-cited quotation, the Examiner is arguing that one skilled in the field would have reasonably expected *additive effects* with the claimed combination. Not only is there no evidence to support that conclusion (*e.g.*, the literature and evidence suggests one skilled in the field would have reasonably concluded the combination would not be advantageous, as was found to be the case with combinations of paclitaxel and 5-FU), but the Examiner's arguments are directed toward additive effects. Each of the claims on appeal recite synergy or greater than additive effects.

Third, the Examiner has not considered the rebuttal evidence submitted in this case in reaching his conclusions. Instead, he has disregarded, and given no credence to, the Declaration submitted by appellant. *Cf. In re Alton*, 37 USPQ2d 1578, 1582 (Fed. Cir. 1996) (examiner erred in refusing to consider effect of appellant's declaration on *prima facie* obviousness case where examiner summarily dismissed the declaration as providing opinion testimony on the ultimate legal question at issue). *See also* MPEP 2144.08 (B) ("Office personnel should consider all rebuttal arguments and evidence presented by applicants" [p. 2100-158] and "should avoid giving evidence no weight, except in rare circumstances" [p. 2100-159]).

Here, the Examiner has summarily dismissed as allegedly irrelevant, appellant's declaration attesting to the surprising and unexpected preclinical, synergistic effects achieved with the claimed combination. Additionally, the Examiner likewise dismisses as irrelevant, and gives no credence to, appellant's literature evidence teaching that combinations of 5-FU plus paclitaxel, a microtubule-stabilizing agent like ixabepilone, are deleterious. (*See* EA, page 10, lines 4-6, and appellant's main brief, page 18). Appellant submits this evidence is highly relevant, as it is evidences the state of the art regarding combinations of 5-FU and microtubule-stabilizing agents, of which ixabepilone is one, at the time of the invention herein.

At page 9, lines 4-7 (EA), the Examiner argues, in response to appellant's position that Danishefsky teaches away from the instantly claimed invention, that "one cannot show nonobviousness by attacking references individually, where the rejections are based on the combination of references". Appellant's reply is that the Examiner misinterprets appellant's arguments on teaching against. Appellant's arguments are directed at what the references teach as a whole. The appellant's argument on teaching against is that it was *not* obvious to pick ixabepilone from the various compounds disclosed in Danishefsky, and to pick 5-FU from the list of various combination agents, and to then engage in further research to evaluate the effects of modifying a combination of ixabepilone and 5-FU to replace 5-FU with capecitabine in a combination with ixabepilone, because Danishefsky teaches against selection of ixabepilone, and thus, would discourage one skilled in the field from further research in evaluating the effects of this compound in combination with other agents, such as capecitabine.

At page 9, lines 11-13 (EA), the "Examiner argues that Danishefsky clearly discloses aza-EpoB as more active in combination with other cytotoxic agents or anticancer agents than the individual drugs alone". Appellant's reply is that this is an incorrect reading of Danishefsky. When properly read as a whole, Danishefsky teaches only therapeutic combinations of epothilone compounds having an olefin at the 12-13 positions, rather than epothilone compounds and analogs having a 12-13 epoxide. For example, in the Summary of Invention section (col. 3), alternative embodiments sections (e.g., cols. 3-8), detailed description section (e.g., cols 30-32), and in all the

claims (cols. 124-132), each and every one of the inventive compounds recited in Danishefsky contain an olefin (double bond group), at the 12-13 position. The inventive compounds of Danishefsky are clearly these olefins. The list of combination agents at column 60 are disclosed for use in combination with "inventive anticancer agents of the present invention" (col 59, lines 61-62). Ixabepilone is not an "inventive anticancer agent of the present invention" in Danishefsky. Ixabepilone is disclosed in Danishefsky only for the sake of disclosing the total synthesis of the compound and for attempting to disparage the effects achievable with the compound in comparison with dEpoB (Danishefsky, col. 100, lines 5 through 45).

In short, the essential premise the Examiner relies on to make his rejection of the present claims over Danishefsky and Miwa simply does not exist. Danishefsky does not disclose what the Examiner argues it discloses. To further illustrate this point, Danishefsky discloses various compounds that are not considered to be "inventive anticancer agents of the present invention", such as, for example, various intermediate compounds at columns 11 and 12. One could not be heard to say Danishefsky discloses these intermediate compounds in therapeutic combinations with one or more agents selected from the list of agents at column 60. The same rings true for ixabepilone. Simply because the structures of the intermediates, and the structure of ixabepilone, are disclosed in Danishefsky, does not mean that Danishefsky discloses them as "inventive anticancer agents of the present invention" to be combined with one or more of the compounds selected from the list of agents at column 60.

At page 10, lines 1-3 (EA), in support of an alleged motivation to combine, the Examiner argues that "Miwa discloses capecitabine to be converted to 5-fluorouracil (5-FU) by dThdpase in tumors, should be much safer and more effective than 5-FU, for treating cancers or various types of tumors (abstract)." Here, the Examiner's reasoning reflects a scientific conclusion. In particular, the Examiner is concluding that, because capecitabine may be considered safer (based on Miwa) than 5-FU, capecitabine can thus be exchanged for 5-FU in any combinations of agents, with the combination then retaining the same effectiveness and increased safety, regardless of what the other agent might be, or its mechanism of action. This conclusion has no evidentiary support in the record and is overly simplistic. It loses sight of the unpredictability and

complicated nature of combination drug therapy, given, for example, drug-drug interactions and mechanisms of action for the agents. *Cf.* MPEP 2144.02 ("when an examiner relies on a scientific theory, evidence support for the existence and meaning of that theory must be provided"), *citing In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979).

Significantly, the Examiner's scientific conclusion on the interchangeability of 5-FU and capecitabine also ignores the evidence of record. Notably, here, the inventor performed studies regarding ixabepilone and its effects on regulating the dThdpase enzyme. These studies resulted in the finding that ixabepilone failed to significantly upregulate levels of dThdpase. *See* Declaration of Francis Lee, ¶ 7. From these findings, the inventor, a Ph.D research scientist with thirteen years of full-time experience in the pharmaceutical industry, concluded that ixabepilone would not have a synergistic effect in combination with capecitabine because his studies demonstrated that ixabepilone failed to significantly increase dThdpase levels in tumors (*Id.*, ¶ 8.) Thus, the very fact that the Examiner relies upon in support of his alleged motivation to combine – conversion of capecitabine to 5-FU *in vivo*, by the dThdpase enzyme – undermines his rejection. That dThdpase enzyme converts capecitabine to 5-FU supports the conclusion it would *not* have been obvious to obtain advantageous therapeutic effects with a combination of ixabepilone and capecitabine, as ixabepilone was found to *not* increase dThdpase levels. (*See id.*, ¶¶ 8, 11, 15).

Lastly, the appellant herein will address the Examiner's reasons for refusing to give any weight to the Lee Declaration. The Examiner has discarded this evidence as irrelevant. (*See*, EA, p. 10, lines 9-16). The Examiner now gives three excuses for refusing to consider this evidence – two are newly raised for the first time in the Examiner's Answer. All three are insufficient grounds to refuse to consider appellant's rebuttal Declaration.

First, the Examiner argues that the Declaration of Dr. Lee, attesting to the surprising results achieved with ixabepilone and capectiabine, should not be considered as the studies Dr. Lee relies upon relate only to preclinical studies with a human colon carcinoma cell line, whereas, in the Examiner's view, "the claims are drawn to various cancers." (EA, p. 10, lines 10-11). However, the claims on appeal are narrowly tailored

to a small group of cancers, namely, "metastatic breast cancer, lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, colon cancer, and/or small cell lung cancer." (*See* claim 117). Additionally, the specification herein reports on preclinical studies and data that was generated with ixabepilone not only in studies involving human colon tumor models, but also with ovarian carcinoma and breast tumor models, with a murine fibrosarcoma model, and with multi-drug resistant tumor models. (*See* specification, page 21, lines 1-19; *see also* specification at page 67, summarizing data and tumor models). Thus, the claims on appeal recite a narrow scope of specific tumors for which data is provided in the specification. That the Declaration provides supportive evidence on synergistic effects as to one of the small group of cancers is not a basis to reject the Declaration entirely as irrelevant. *See, e.g.,* MPEP 2144.08 ("When considering whether proferred evidence is commensurate in scope with the claimed invention, Office personnel should not require the applicant to show unexpected results over the entire range of properties possessed by a chemical compound or composition") *citing In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987).

The second rationale the Examiner has provided to dismiss the Lee Declaration, which is raised for the first time in the Examiner's Answer, is that "there is only one data point in the Declaration drawn to 10 mg/kg of compound (1) and 250 mg/kg/adm of capecitabine, whereas the claims are drawn to all dosage ranges of both compound (1) and capecitabine." (EA, page 10, lines 12-14.) However, the tests reported in the Lee Declaration were performed on mice. These were preclinical tests used to evaluate the combinatory effects. The drugs were administered at their maximum tolerated dosages for a number of days, sequentially (*See* Lee Declaration, ¶ 11). Administering the drugs at their maximum tolerated dosages is typical in preclinical studies of this nature, which are designed to gather *in vivo* preclinical data. However, applicant cannot then be expected to limit its claims to the dosages administered to the mice for the data to be considered.

The Examiner's reasoning in this regard lacks logic and would undermine the ability of patent applicants to rebut rejections on method of treatment claims, and would render such claims essentially meaningless. If the Examiner's reasoning were accepted, taken to its logical extreme this would mean that any time a method of

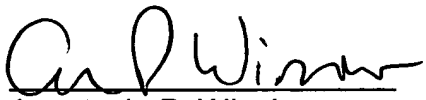
treatment claim were rejected, *e.g.*, for obviousness or lack of enablement, and the applicant sought to rebut the rejections with *in vitro* or *in vivo* data, the data could be rejected if the dosages used in the *in vitro* or *in vivo* tests did not correspond with specific dosages set forth in the method of treatment claims. Again, under *In re Chupp*, 2 USPQ2d at 1439, this is not the law as the patent applicant in a rebuttal declaration is not required to provide results over the entire claim scope in order for the declaration to be considered.

Finally, the third reason the Examiner raises to dismiss the Lee Declaration (also raised for the first time in the Examiner's Answer), is that "the Declaration clearly provide only a delay in tumor growth, while the claims are drawn to treating cancer, which is construed as both inhibition and regression of cancer." (EA, page 10, lines 14-16.) The Examiner is here again making a scientific conclusion without evidentiary support. In this case, his conclusion – that cancer treatment requires regression and inhibition of the cancer – is plain wrong. Not all chemotherapeutic agents are designed to both arrest the growth of cancer cells and kill cancer cells. Some agents are designed to inhibit intracellular signaling so as to interfere with uncontrolled cell growth, but may produce little or no cell killings. The effect of these agents may be to inhibit proliferation of tumor cells while cell death continues (via apotosis), leading to gradual involution of the tumor. (The appellant is prepared to submit evidence on this point but will not do so for the first time in the appeal brief, as contrary to the rules.) In any event, the Examiner has erred in refusing to give any weight to appellant's Declaration based on a scientific theory on the meaning of the word "cancer treatment," without evidentiary support on his interpretation of "cancer treatment," and by raising this unsupported theory for the first time in the Examiner's Answer.

CONCLUSION

For all the foregoing reasons, as well as those set forth in appellant's main Appeal Brief filed May 25, 2006, appellant respectfully requests that the rejection of claims 117 through 130 herein be reversed and that claims 117 -130 stand allowed. Alternatively, appellant respectfully requests that the rejection of claims 117 through 130 be reversed and that prosecution be re-opened with directions that appellant's evidence be fully considered, and so that the Examiner's scientific arguments raised on appeal can be rebutted.

Respectfully submitted,



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